UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,894	09/22/2004	Ajita Bhat	P51328	9704

20462 7590 02/05/2007

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,894	BHAT ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-72 and 92-104* is/are pending in the application.

4a) Of the above claim(s) *65,67,70 and 92-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-64,66,68,69,71 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Lack of Unity of Invention

A finding of Lack of Unity of Invention was mailed to applicants' counsel on 25 October 2006. In the reply to the finding, filed 28 November 2006, applicants indicated election of Group I, drawn to compounds *per se*, of Formula (I), and a pharmaceutical composition comprised of the compounds. Election was made with traverse, but no explanation as to why applicants believe the examiner erred in finding unity of invention to be lacking in the instant case. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse, as was explained on page 6 of the Finding, first full paragraph (also, see MPEP § 818.03(a)).

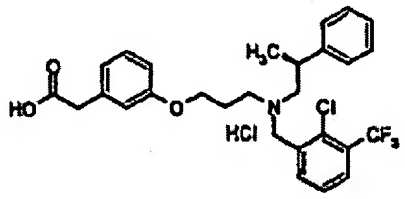
Applicants' amendment filed with the response to the finding has cancelled all claims not in Group I, so the requirement is technically moot. However, new claims 92-104 correspond to the subject matter of Groups II and III as set forth in the Finding of Lack of Unity of Invention, and as such stand withdrawn from consideration as being drawn to nonelected subject matter, pursuant to 37 C.F.R. 1.142(b).

As requested by applicants in the reply to the Finding of Lack of Unity of Invention (and as stated in the Finding, pages 6 and 7), method of use claims which depend from an allowable product claim, at such time that there is an allowable product claim, will be rejoined and the Finding of Lack of Unity of Invention between the two will be withdrawn.

The finding of Lack of Unity of Invention included a further requirement for applicants to elect a single disclosed specie of whichever invention is elected. For the invention of Group I, this election of specie requirement would correspond to election of a

single chemical compound included in the scope of that invention Group. In response to this requirement, election of the compound of Example 10 in the instant specification was indicated. It is the tenth compound specified in instant claim 68, twentieth in claim 69. This compound is represented by the following name and structure diagram:

Example 10
(S)-2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2-phenyl-propyl)amino]propoxy}-phenyl)acetic acid hydrochloride salt



In the elected species, "Z" is a carbon atom, "Y" is an oxygen atom, m=1, W^3 is H, W^2 is alkyl (methyl) and W^1 is aryl (phenyl), q=1 and "Q" is aryl (phenyl). "X" is the group –$COOR^{10}$ wherein R^{10} is H, p=1 and t=0. A search of the prior art, based on the structure of the elected species compound, was begun. Only compounds of Formula (I), wherein X=COOH, p=1-8, Y=-O-, and at least one of W^1, W^2 and W^3 is phenyl, wherein all other variables are as defined in Formula (I), were the subject of the search. Prior art rendering Formula (I) compounds unpatentable was found, whereupon the search was stopped.

In accordance with "Markush practice" outlined in MPEP 803.02, all claims not readable on the elected species compound have been withdrawn from consideration, because art rendering the Markush-type claim unpatentable was found. These claims, not readable on the compound of Example 10 from the instant specification, are claims 65, 67 and 70.

In total, claims 67, 70 and 92-104 have been withdrawn from consideration at this time. No claim has been completely searched.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-66, 68, 69, 71 and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula (I) compounds, pharmaceutically acceptable salts thereof, in the form of stereoisomers, mixtures of stereoisomers, or racemates, does not reasonably provide enablement for solvates of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

When making the determination of whether a claimed invention is enabled by the accompanying specification, factors identified in the decision rendered by the Court in *In re* Wands are relied upon. These so-called "Wands factors" are:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each of the factors will be addressed with respect to the claimed solvates of Formula (I) compounds –

(A) Insofar as the solvate embodiment of claims 49-66, 68, 69, 71 and 72 is concerned, those claims read on solvates of compounds according to Formula (I), with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug."

(B) The nature of the invention is that of a chemical compound in a special physical form.

(C), (D), (E) At the time the invention was made, solvates were of course known, and much was understood about how and why solvates form, but the skilled chemist's understanding of solvates was not such that the directed preparation of those solvates other than hydrates was routine or simple. Most of the research on solvates has been focused on characterization of solvates after they are discovered, which is most often by accident. Efforts to devise mathematical models for prediction of solvate structure or whether or not certain solvates are chemically possible have not been successful. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of Formula (I) is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a definition of what the word "solvate" means (page 14, lines 14-21), there is no description of solvates in the specification.

(G) No working examples demonstrate the preparation of a solvate. In fact, compounds of the invention are crystallized from a variety of solvents throughout the working examples, yet not solvate of any compound with any of the solvents employed is identified. Thus, it is clear that simply bringing the compound into contact with a solvent will not afford the claimed solvates. Special conditions and special compound/solvate combinations are required, which cannot be predicted in advance.

(H) Manufacture of only a small fraction of the total of each compound of Formula (I), as a solvate with every solvent within the scope of the term "solvate" generally, would represent the efforts of many over a period of years. Those efforts are potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. Applicants' right to exclude others from making all solvates of compounds according to Formula (I) is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

Claims 49-66, 71 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 49, from which all of 50-66, 71 and 72 depend at least indirectly, there are no definitions for the terms "Ar" and "Het." The claims have been examined on the merits as though "Ar" stood for aryl and "Het" stood for heteroaryl, but this is only a guess. Applicants must clearly define these two terms.

Claims 71 and 72 are indefinite, in addition to being indefinite for depending from an indefinite base claim (claim 49). A pharmaceutical composition, as is specified in claim 71, includes some pharmaceutically acceptable carrier material or diluent by definition, else it is the drug in the pure form, the compound *per se*. So, claim 72, which depends from claim 71, and further specifies "comprising a pharmaceutically acceptable carrier or diluent" renders the scope of both claims ambiguous. Additionally, if it is assumed that

claim 71, absent the pharmaceutically acceptable carrier or diluent, actually is the compound of claim 49 *per se*, then claim 71 is a substantial duplicate of claim 49.

Cancellation of claim 72, and incorporation of the limitation "and a pharmaceutically acceptable carrier or diluent" at the end of claim 71 is recommended.

Claims 68 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In independent claim 68, from which claim 69 depends, the series of compounds is set out with each compound being separated from the preceding and following ones by semicolons. At page 14 (of the claims as were presented with the amendment filed 28 November 2006), lines 2 through 16, however, commas appear instead of semicolons. The significance, if any, of this change in the manner of separating compounds' names is not understood. To avoid the possibility of ambiguity, it is recommended that claim 68 be amended such that all compounds are recited with semicolons between compounds' names. Claim 68 is further indefinite because the recitation at the end of the claim "and a stereoisomer, a stereoisomer mixture or racemate thereof..." is contradictory to some of the subject matter specified in the claim. Many of the compounds named in claim 68 are designated as stereoisomers, the single isomer, that is. These pure isomer compounds *cannot* exist as racemates.

Claim 69 is indefinite by virtue of depending from an indefinite base claim, and also includes the contradictory language "racemate mixture thereof" while single isomer compounds are named in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 49-64, 66, 68, 71 and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by United States Patent Application Publication 2004/0072868 (Collins et al). The Collins et al application includes a domestic priority claim to the filing date of U.S. provisional application 60/233,144, which date is 18 September 2000, before the filing date of the instant application. The inventive entities in the respective applications are different.

Collins et al discloses LXR agonists, some of which are embraced by Formula (I) of instant claims 49-64 and 66 in the examples. One of these compounds is specified in claim 68. The compound is disclosed as one of the preferred LXR agonist compounds according to the invention disclosed in the publication, on page 7 of the publication, section [0121], and the synthesis of the compound is described in Example 18, on page 19.

This compound is embraced by instant claims 49-66 wherein Z is a carbon atom; p=1; X is $-COOR^{13}$ where R^{13} is H; k=0; Y is -O-; n=3; t=0; q=1; Q is a phenyl ring substituted with one halogen atom (chlorine) and one alkyl group substituted with three halogen atoms (trifluoromethyl); m=1; W^1 is aryl (phenyl); W^2 is H; W^3 is aryl (phenyl); R^6,

R^7, R^8 and R^9 are each H. This compound is not excluded from the scope of instant claim 49 because W^3 is not H.

The compound of Example 18 from Collins et al is specified instant claim 68, the second named compound.

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49, 71 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 22 of copending Application No. 10/508,791. Although the conflicting claims are not identical, they are not patentably distinct from each other because the second compound specified in claim 22 of the copending application (which is an independent claim), is embraced by instant claim 49 wherein Z is a carbon atom; p=0; X is $-N(R^{17})COR^{13}$, wherein both R^{17} and R^{13} are methyl; Y is -O-; n=3, t=0, m=1, q=1; W^1 and W^2 are phenyl, W^3 is H; Q is phenyl,

substituted with chloro and trifluoromethyl. Synthesis of the compound is described in Example 39 of the instant application. Since the copending application teaches the compounds disclosed therein to have utility as therapeutic agents, drugs, that is, a pharmaceutical composition comprised of a compound according to claim 22 of the copending application is obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Comments

The elected species – the compound of example 10 in the specification, is free of the prior art. Upon rejoinder of now-withdrawn 92-104, rejection of the method specified in those claims, under 35 U.S.C. 112, for lack of enablement, will be necessary. All forms of inflammation, which is what is covered by the recitation of "inflammation" in claim 92, cannot be treated with a single therapeutic agent having a singular biological effect. Inflammation results for a great many disparate physiological processes, many which may not have any thing at all to do with LXR's. So, to aver that all forms of inflammation could be treated with an LXR agonist is contrary to medical science.

Claim 92 does not include a subject to whom the compound of claim 49 is administered.

Prevention of inflammation is not enabled by the disclosure, nor is prevention of atherosclerosis.

The following amended claim 92 would be allowable upon rejoinder with an allowable claim 49 (or some other base claim drawn to compounds which are allowable):

92. A method for the treatment of an LXR mediated disease or condition, wherein said disease or condition is atherosclerosis, comprising administering a therapeutically effective amount of the compound according to claim 49 to a subject in need thereof.

Copending application serial number 10/509,197 includes some of the same subject matter in the claims as the instant application. Specifically, claims 1-8 as they serve as base claims for claim 11 renders the instant method of treatment claims obvious. In the specification of the copending application (page 49, Example 5), the generic structure depicted in claim 11 of the copending application is defined as being inclusive of the same compound which was elected as the species of the invention of Group I, which is of course embraced by the method of treatment claims in the instant application.

So, upon rejoinder of method of treatment claims in the instant application, an obviousness-type double patenting rejection will be necessary, of instant claims 92-104 as being unpatentable over claims 1-8 and 11 of copending application serial number 10/509,197.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

ZACHARY C. TUCKER
PRIMARY EXAMINER